Exhibit 11

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Selective distribution of porphyrins in skin thick basal cell carcinoma after topical application of methyl 5-aminolevulinate

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Abstract

Topical photodynamic therapy (PDT) of superficial basal cell carcinoma (BCC) with 5-aminolevulinic acid (ALA) has achieved promising clinical results. However, the efficacy of this therapy for thick BCC is dramatically decreased by a limited diffusion of hydrophilic ALA into the tumor. Lipophilic esters of ALA may enhance their penetration into the lesion. In this randomized, open clinical study, microscopic fluorescence photometry incorporating a light-sensitive thermo-electrically cooled charge-coupled device (CCD) camera was employed to investigate the penetration of methyl 5-aminolevulinate-induced porphyrin fluorescence in thick BCC lesions. Both the distribution pattern and the amount of porphyrins in 32 lesions of 16 patients were studied after topical application of 16, 80 or 160 mg/g of methyl 5-aminolevulinate for 3 or 18 h. A highly selective and homogeneous distribution of methyl 5-aminolevulinate-induced porphyrin fluorescence was seen in all lesions studied, with much less fluorescence in the adjacent normal skin tissues. In lesions of up to 2 mm thickness the application of 160 mg/g methyl 5-aminolevulinate for 3 h showed the highest ratio of porphyrin fluorescence depth to tumor depth (0.98±0.04), thus providing a biologic rationale for a clinical PDT trial with this regimen.

Keywords: Basal cell carcinoma; Photodynamic therapy; Methyl 5-aminolevulinate; Porphyrin; Fluorescence; CCD camera

1. Introduction

Nonmelanotic skin cancer, primarily basal cell carcinoma (BCC), represents a major health concern [1,2]. BCC arises from the basal cell layer of the epidermis or its appendages. Current treatment for the disease includes Mohs'micrographic surgery, local excision, curettage and electrodesiccation, cryosurgery, radiotherapy and immunotherapy. Mohs' micrographic surgery may be suitable for large and infiltrating BCC lesions, while excisional surgery is used for small BCCs. Other modalities can be applied to patients in whom surgery is contraindicated. The goal of the treatment to be chosen is to provide patients with the safest, most cost-effective and curative therapy. However, none of the available methods are ideal with respect to convenience, cosmetic outcome and cost.

Photodynamic therapy (PDT) of cancer has developed during the past 25 years to become an important new clinical treatment modality [3]. This modality typically involves systemic administration of a tumor-localizing photosensitizer. Subsequent activation of the photosensitizer by visible light mediates singlet oxygen-induced tumor destruction [3]. Photofrin-based PDT has recently been approved by regulatory agencies in many countries for several medical indications [3], and has also been applied successfully in dermatologic malignancies [4–6]. However, like most photosensitizers, Photofrin-PDT has a major side-effect of skin phototoxicity.

Because of the side-effects of Photofrin-PDT, considerable interest has recently been directed towards developing a new PDT regimen that relies on an endogenously synthesized sensitizer [7–9]. In the first step of the heme biosynthetic pathway, 5-aminolevulinic acid (ALA) is formed from glycine and succinyl CoA. The last step is the incorporation of iron into protoporphyrin IX (PpIX, a potent photosensitizer), which takes place in the mitochondria under the action of the enzyme ferrochelatase. By adding exogenous ALA, the naturally occurring PpIX may transiently accumulate because of the limited capacity of ferrochelatase. Furthermore, the activity of porphobilinogen deaminase, another enzyme of the heme synthesis

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pathway (catalyzing the formation of uroporphyrinogen from porphobilinogen), is higher in some tumors [10,11], while that of ferrochelatase is lower [10,11], so that PpIX accumulates with a high degree of selectivity in these tumors. Such selectivity has therefore been exploited for its application in PDT of tumors as an alternative to administration of exogenous photosensitizers [7–9].

Encouragingly, PDT with topical application of ALA has recently achieved promising results in the treatment of superficial cutaneous diseases (e.g. actinic keratosis and superficial BCC) [9]. However, the efficacy of the treatment for thick BCC lesions is dramatically decreased due to the limited penetration of hydrophilic ALA into the lesions [12,13]. ALA esters with an increased lipophilic nature may thus enhance their penetration into diseased tissues and be more suitable for topical application to skin thick lesions [14–23].

The aim of the present study was to determine the optimal dosage and application time of Metvix® cream containing methyl 5-aminolevulinate in thick BCC lesions, the information crucial for further PDT use.

2. Materials and methods

2.1. Patients

Sixteen patients with a total number of 44 clinically diagnosed thick BCCs were included in this open, randomized, controlled study during the period September 1997 to August 1998. To be considered eligible, patients must have had one to three previously untreated thick BCC lesions. Patients with pigmented BCC, Gorlin syndrome, squamous cell carcinoma and malignant melanoma were excluded. All patients were given verbal and written information on the nature of the study, and provided written consent prior to the start of the study procedures. The investigation was approved by the Regional Ethics Committee, Health Region II, Norway, and the Norwegian Medicines Control Authority.

2.2. Drug

Metvix cream containing methyl 5-aminolevulinate at concentrations of 16, 80 and 160 mg/g was supplied by PhotoCure ASA (Oslo, Norway) in 2 g collapsible aluminium tubes.

2.3. Treatment procedure

Each lesion was randomly allocated to one of the topical applications with 16, 80 or 160 mg/g methyl 5-aminolevulinate for 3 or 18 h. In a patient with up to three lesions the same application time, but with different concentrations of methyl 5-aminolevulinate, was applied according to the randomization. The methyl 5-aminolevulinate Metvix cream was applied to a lesion as an approximately 1 mm thick layer and 1 cm outside the lesion. It was covered with an occlusive dressing (Tegaderm®, 3M) for 3 or 18 h, after which the cream was washed off and a biopsy was taken to determine the penetration depth and production of methyl 5-aminolevulinate-induced porphyrins. All of the treated biopsies were processed for light microscopy and examined histologically, and only lesions thicker than 0.5 mm (defined as thick BCC in the present study) were included for further porphyrin fluorescence imaging analysis.

2.4. Preparation of tissue samples

Each biopsy was performed in such a way that both the tumor and the surrounding normal skin tissues were included. Once removed, the samples were immediately immersed in liquid nitrogen and stored in a freezer at −80°C. The tissue blocks were mounted in medium (Tissue Tek II embedding compound, BDH, Poole, UK), and the tissue sections were then cut with a cryostat microtome to a thickness of 8 μm and mounted on clean glass slides. Because of the diverse tumor depths a large number of serial sections were cut from each tissue block. Only the sections that showed, under a transmission microscope, the maximum depth of the tumor (prior to hematoxylin and eosin staining) were used for fluorescence measurement. The fluorescence images of methyl 5-aminolevulinate-induced porphyrins were directly made by means of microscopic fluorescence photometry. The same frozen sections were subsequently stained with H&E for histologic identification.

2.5. Microscopic fluorescence photometry

Microscopic fluorescence photometry was carried out using an Axioplan microscope (Zeiss, Germany) with a 100 W mercury lamp. The fluorescence images were made by a highly light-sensitive thermo-electrically cooled charge-coupled device (CCD) camera. The resolution was 385×578 pixels with a dynamic range of 16 bits per pixel (Astromed CCD 3200, Cambridge, UK). The filter combination used was composed of a 390–440 nm excitation filter, a 460 nm beam splitter and a 630±20 nm band-pass emission filter. A rectangular area superimposing the lesion zone (with maximal depth) from the most superficial layer to the bottom layer was made on each fluorescence image. The fluorescence intensity within the selected area was then quantified as a function of depth of the lesion by an image processing unit (Astromed/Visilog) and plotted by SigmaPlot. The mean value of the specific porphyrin fluorescence intensity per pixel (0.23 pixel/μm, a lateral resolution of 10 μm) was calculated in an area every 200 μm of tumor depth. The same lens (4×) and integrated exposure time (15 s), which result in less than 5% photobleaching of the porphyrin fluorescence, were used

throughout the whole study. The measurement was also corrected for nonuniform illumination of the lamp as well as for the background of tissue autofluorescence in BCC samples receiving no methyl 5-aminolevulinate. The amount of porphyrin formation in normal skin adjacent to the lesion was also studied. The fluorescent imaging work was carried out in a blind manner with respect to the concentration and application time of methyl 5-aminolevulinate.

2.6. Safety

Adverse events were recorded 1 and 6–8 weeks after topical application of methyl 5-aminolevulinate. In addition, blood samples for tests of white blood cells, platelets, sedimentation rate, sodium, potassium, creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphates, γ-glutamyl transpeptidase (γ-GT), hemoglobin and bilirubin were taken before and 7 days after the treatment.

2.7. Statistical analysis

A two-way ANOVA method was used to analyse the data on tumor depths between the 3 h and 18 h groups and on the penetration depths of porphyrin fluorescence in tumors treated with various concentrations of methyl 5-aminolevulinate for 3 and 18 h. All tests were performed at the 0.05 significance level.

3. Results

3.1. Patients and lesions

The age and sex distributions of the 16 patients are shown in Table 1. Initially, a total number of 44 clinically diagnosed thick BCC lesions were included, but 12 lesions were histopathologically confirmed to be thinner than 0.5 mm and were thus excluded. Information on the remaining 32 thick lesions treated is also presented in Table 1. Although randomly allocated, the tumors treated for 3 h were significantly deeper than those treated for 18 h.

Table 1
Information on patients and BCC lesions

	3 h application time ($n = 8$)	18 h application time ($n = 8$)
Age (years) mean±S.D. (range)	67.2±8.8 (52–76)	71.5±11.2 (54–86)
Sex		
Male	5	6
Female	3	2
Total No. of lesions included	21	23
No. of lesions verified by histopathology as thick BCC	16	16
No. of lesions per patient		
One	1	0
Two	1	1
Three	6	7
No. of verified thick lesions per dose of methyl 5-aminolevulinate		
16 mg/g	5	5
80 mg/g	5	5
160 mg/g	6	6
Localization of verified thick lesions		
Head/face	2	0
Truncus/neck	9	11
Extremities/shoulder	5	5

3.2. Distribution of porphyrins induced by methyl 5-aminolevulinate in thick BCC lesions

In untreated tissues, the intensity of the autofluorescence as background was measured to be 668±36 (mean±S.D.) and levels >740 (mean+2S.D.) were then defined as the specific porphyrin fluorescence induced by methyl 5-aminolevulinate. Fig. 1 shows a typical fluorescence image obtained from a lesion treated topically with methyl 5-aminolevulinate (160 mg/g, 3 h). The rectangular area visualized on the image depicts the area where the porphyrin fluorescence intensity was measured. In general, porphyrin fluorescence induced by methyl 5-aminolevulinate was highly selectively and homogeneously distributed in the lesions. The biopsies treated with 16, 80 or 160 mg/g methyl 5-aminolevulinate for 3 h induced less porphyrins than those treated with the corresponding concentrations for 18 h (Table 2). The relative depth of porphyrin fluorescence is defined as the ratio of the depth of porphyrin fluorescence to the depth of the tumor. The distribution of porphyrin fluorescence at various depths of the lesions is presented in Table 2 and the relative depth of porphyrin fluorescence in Table 3. The application of 160 mg/g reached the highest ratio (0.98±0.04) in the 3-h group and was shown to be significantly better than both the 16 mg/g ($P=0.03$) and 80 mg/g ($P=0.03$) regimens. In the 18-h group, treatment with 80 mg/g resulted in the best ratio of 0.88±0.22, but no significant difference among the regimens with respect to the various concentrations was found ($P=0.33$). It should be pointed out that there was a large variation in the porphyrin fluorescence distribution among individual lesions within a group as well as among the various groups (Tables 2 and 3). As expected, there was no significant methyl 5-aminolevulinate-induced porphyrin fluorescence in normal der-

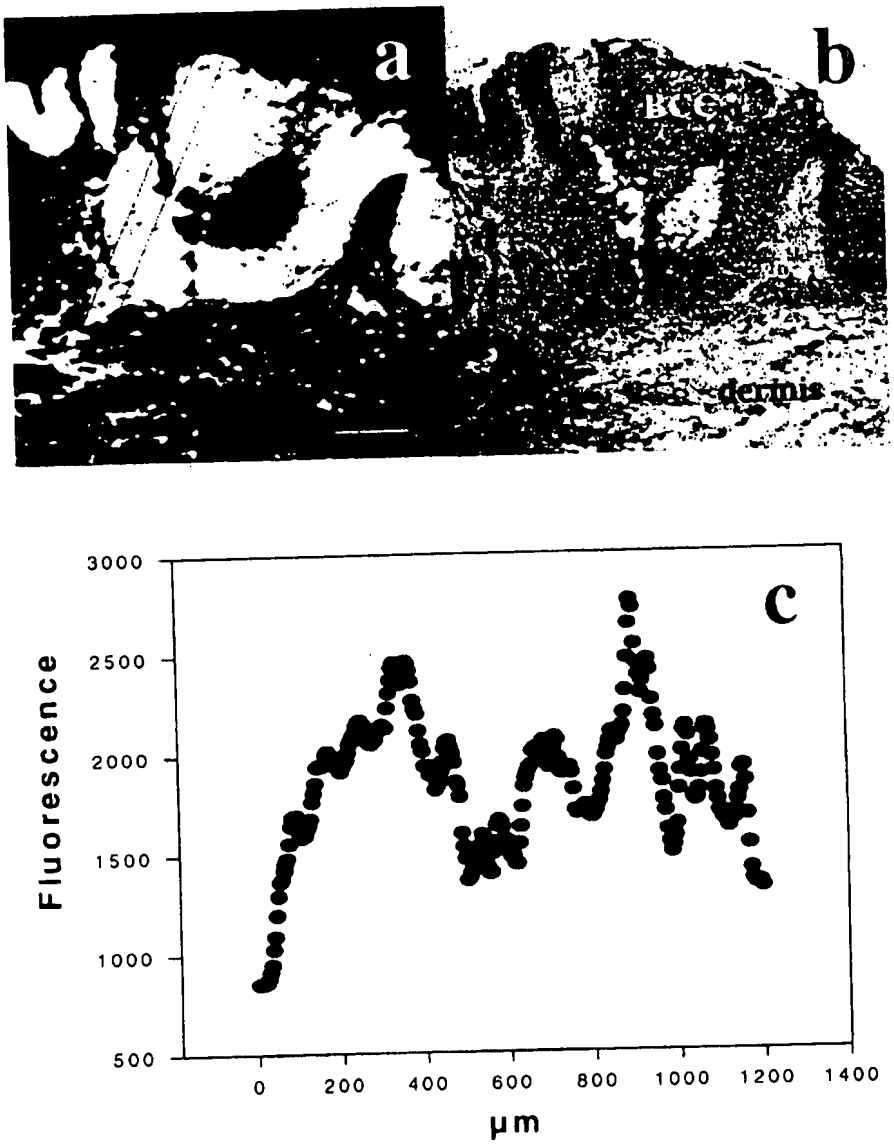

Fig. 1. Fluorescence (a) and corresponding transmission (b) microphotographs of a thick BCC taken 3 h after topical application of 160 mg/g methyl 5-aminolevulinate, showing the porphyrin fluorescence in the whole lesion. The bar in (a) is 300 μm. (c) Fluorescence intensity of the superimposing area shown in (a) plotted as a function of the tumor depth from the most superficial layer to the bottom.

mis, since the dermis is mainly composed of fibro-connective tissue with few cellular components.

3.3. Porphyrin formation in normal skin

Porphyrin formation was observed in the surrounding normal epidermis after topical application of methyl 5-aminolevulinate, although much less than in BCC lesions. It is evident that, with all the concentrations of methyl 5-aminolevulinate studied, application for 18 h produced far more porphyrins than for 3 h in the normal skin.

3.4. Adverse reactions and laboratory changes

Neither adverse clinical events nor relevant changes in laboratory tests were observed during the study.

4. Discussion

The application of PDT to premalignant and malignant diseases in dermatology has been recognized for a long

Table 2
Specific porphyrin fluorescence at different depths of the lesion (mean±S.E.)[a]

Depth (μm)	3 h			18 h		
	16 mg/g	80 mg/g	160 mg/g	16 mg/g	80 mg/g	160 mg/g
0–200	146±19 (4[b])	144±20 (4)	228±21 (6)	146±14 (5)	456±44 (5)	171±15 (6)
201–400	318±20 (4)	354±27 (4)	345±32 (6)	490±8 (2)	695±94 (5)	441±43 (6)
401–600	460±37 (4)	355±18 (4)	324±29 (6)	404±6 (2)	658±110 (5)	543±38 (3)
601–800	177±2 (4)	202±11 (4)	262±25 (6)	188±14 (2)	635±96 (4)	640±99 (3)
801–1000	12±1 (3)	189±13 (4)	382±31 (6)	163 (1)	381±55 (4)	332±32 (3)
1001–1200	[c]	230±16 (3)	373±15 (5)	30 (1)	461±242 (3)	164±85 (3)
1201–1400	[c]	74±3 (3)	262±4 (4)	[c]	822 (1)	177 (1)
1401–1600	[c]	[c]	116±3 (2)	[c]	[c]	39 (1)
1601–1800	[c]	[c]	114±4 (2)	[c]	[c]	40 (1)
1801–2000	[c]	[c]	46 (1)	[c]	[c]	108 (1)

[a] Background (740) of tissue autofluorescence was subtracted from all data.
[b] Number of measurements.
[c] No porphyrin fluorescence or no deeper lesions measurable.

time [3]. PDT with systemic application of Photofrin is an effective modality for treating superficial cutaneous tumors [9]. However, the main disadvantage of using Photofrin-PDT is the risk of prolonged skin phototoxicity. PDT based on topically applied ALA has recently shown promising results in the treatment of superficial skin disorders [9]. It is an easy and cheap procedure with no risk of cutaneous photosensitization. Topical ALA-PDT is, however, inefficient at treating thick BCC, with only about 50% cure rates achieved [9]. The reason for this is not entirely known, but our previous study has shown a very limited penetration of ALA-induced porphyrins into thick BCC lesions after topical application of 20% ALA for 3 h [12]. Similar results were also reported by others [24].

The present study demonstrates that porphyrin fluorescence induced by methyl 5-aminolevulinate is selectively and homogeneously distributed in thick BCC lesions with little fluorescence seen in the dermis (Fig. 1). Furthermore, topical treatment with 160 mg/g methyl 5-aminolevulinate for 3 h or 80 mg/g for 18 h produced an adequate depth of porphyrin fluorescence throughout the thick tumors. The relative depth of porphyrin fluorescence for the two regimens was 98 and 88%, respectively, indicating an apparent improvement in the penetration depth of porphyrins into thick tumors compared with the other treatment regimens studied. This is also supported by our recent finding that a complete response rate of 82.4% was obtained after a 3-month follow-up in a group of 273 thick BCC lesions that had been PDT-treated with a 3-h topical application of 160 mg/g methyl 5-aminolevulinate following surface removal.

Table 3
Depth of porphyrin fluorescence in lesions

	3 h	18 h
Lesion depth (mm) per dose of methyl 5-aminolevulinate: mean±S.E. (range)		
16 mg/g	1.5±0.26 (0.7–2.2)(5)[a]	1.0±0.09 (0.8–1.2)(5)
80 mg/g	1.6±0.21 (1.0–2.0)(5)	1.1±0.07 (0.9–1.3)(5)
160 mg/g	1.4±0.22 (0.6–2.0)(6)	1.2±0.16 (0.9–1.9)(6)
Depth of porphyrin fluorescence (mm) mean±S.E. (range)		
16 mg/g	0.7±0.18 (0.0–1.0)(5)	0.5±0.19 (0.2–1.1)(5)
80 mg/g	1.0±0.26 (0.0–1.4)(5)	1.0±0.11 (0.6–1.3)(5)
160 mg/g	1.3±0.21 (0.6–2.0)(6)	0.8±0.24 (0.4–1.9)(6)
Relative depth of porphyrin fluorescence (%) mean±S.E. (range)		
16 mg/g	55.7±16.4 (0–100)(5)	52.0±19.7 (16.7–100)(5)
80 mg/g	61.5±17.5 (0–100)(5)	88.2±9.7 (50–100)(5)
160 mg/g	98.3±1.7 (90–100)(6)	66.9±14.9 (25–100)(6)

[a] Number of subjects measured.

The normal epidermis showed much less methyl 5-aminolevulinate-induced porphyrins than the surrounding BCC lesions. This selectivity of methyl 5-aminolevulinate-induced porphyrins in the tumor is of clinical importance since it can reduce the phototoxic reactions of local healthy tissue to PDT. In addition, the production of porphyrins induced by methyl 5-aminolevulinate in normal epidermis is also dependent upon the application time. Application for 3 h induced much less porphyrins in normal epidermis than for 18 h, demonstrating a possibly reduced tumor selectivity of the porphyrins with a longer application time.

In conclusion, the application of 160 mg/g methyl 5-aminolevulinate for 3 h can induce porphyrin formation throughout the depth of thick BCC lesions (up to 2 mm) with high selectivity. This regimen should thus be explored for the photodynamic treatment of thick BCC in clinical trials.

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